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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,397	02/08/2000	Gerald Soff	4228-1-1-1	2549

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/500,397	SOFF ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 23-75* is/are pending in the application.

4a) Of the above claim(s) *1-18 and 25-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4,5,8* (5 sheets)
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of group V, claims 19, 22-24, species captopril, and tissue plasminogen activator in Paper No. 9 is acknowledged. The traversal is on the ground(s) that 1) groups IV and V should be combined, because both are classified in the same class 514 and subclass 2, and there is no serious burden for the Examiner to examine them together, and because groups IV and V are not independent and patentably distinct according to MPEP 802.01, 2) groups XXI and XXII should be examined together because they were not restricted in the parent US PN= 6,024,688, both classified in the same class 514 and subclass 2, because there is no serious burden for the Examiner to examine them together, and because groups XXI and XXII are not independent and patentably distinct, 3) the species of the sulfydryl donor are linked by a generic claim (claim 19) which links a reasonable number of species, 4) the species of the plasminogen activator are linked by a generic claim (claim 19) which links a reasonable number of species.

After review and reconsideration, groups XXI and XXII will be combined, because it would not be a serious burden for the Examiner to examine them together. Groups IV and V however are not combined, because the methods of groups IV and V use different reagents, wherein the method of group V uses an additional reagent, a plasminogen activator, the properties and function of which are completely different from the reagent sulfhydryl donor used in group IV. In addition, the searches for these groups are complex, based on different databases, and not just based on their classification. Therefore, groups IV and V are independent and patentably distinct, the

searches for the two groups are not co-extensive, and it would be a serious burden for the Examiner to examine them together. Moreover, the species of the sulfhydryl donor or the plasminogen activator are patentably distinct, and not combined because they are linked by a Markush grouping (claims 20 and 23), and because they have different structure and properties.

In addition, Applcant amends claim 19 and cancels claim 22, and states that in view of the amendment of claim 19, claim 21, which is dependent on claim 19, should be examined together with the amended claim 19.

After review and reconsideration, claim 21 will be examined with the amended claim 19.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 19-21, 23-24, species captopril, and tissue plasminogen activator are examined in the instant application.

PRIORITY DATE

The Examiner has established a priority date (02/08/2000) for the instantly claimed application serial number 09/500397 as the applications SN=08/991761, 08/710305 to which priority is claimed does not recite the limitation "a method of treating an angiogenic disease, comprising administering a plasminogen activator and 'optionally' an amount of a sulfhydryl donor". Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

REJECTION UNDER 35 USC 101, DOUBLE PATENTING

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19, 20, 23 are provisionallly rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 65-68 of US Application Serial No. 08/991761.

Claims 19, 20, 23 of of US Application Serial No. 09/500397are drawn to a method for treating an angiogenic disease comprising administering a plasminogen activator, and optionally a sulfhydryl donor, wherein the plasminogen activator is selected from the group consisting of urokinase, streptokinase and tissue plasminogen activator and wherein the sulfhydryl donor is selected from the group consisting of cysteine, N-acetyl cysteine, captopril, D-penicillamine and reduced glutathione.Claims 65, 66-68 of US Application Serial No. 08/991761 are drawn to a method for treating a neoplastic disease comprising administering a plasminogen activator, and optionally a sulfhydryl donor, wherein the plasminogen activator is selected from the group consisting of urokinase, streptokinase and tissue plasminogen activator and wherein the sulfhydryl donor is selected from the group consisting of cysteine, N-acetyl cysteine, captopril, D-penicillamine and reduced glutathione. Although the conflicting

claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The instant claims are generic to the claims of the copending application and would have been obvious in view of the copending claims which have all of the characteristics of a method of treating a neoplastic disease, which is an angiogenic disease.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented

Claim Rejections - 35 USC § 112 SECOND PARAGRAPH

Claims 21, 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 24 are indefinite, because it is not clear an amount of effective plasmin or plasminogen is effective for what.

Claim Rejections - 35 USC § 112 FIRST PARAGRAPH, SCOPE

Claims 19-21, 23-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating cancer, comprising administering a plasminogen activator with or without administrating a sulfhydryl donor, does not reasonably provide enablement for a method for treating an angiogenic disease, comprising administering a plasminogen activator with or without administrating a sulfhydryl donor. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 19, 21, 23-24 are drawn to a method for treating an angiogenic disease comprising administering a plasminogen activator, and optionally a sulfhydryl donor, wherein the plasminogen activator is tissue plasminogen activator, and wherein plasminogen or plasmin is also administered.

Due to the language "optionally", claims 19, 21, 23-24 encompass a method for treating any angiogenic disease comprising administering a plasminogen activator, with or without a sulfhydryl donor, wherein the plasminogen activator is tissue plasminogen activator.

The specification discloses in example 8, case # 2 (pages 48-51), that patients receiving a single treatment with urokinase alone or in combination with captopril, have more than 80% of tumor regression. The specification further discloses that in figure 17A, a marked increase in angiostatin levels is observed in plasma of patients after of treatment of either urokinase alone or in combination with captopril. The specification also discloses that angiostatin purified from plasma of said patients using a lysine affinity column reduces growth of aortic endothelial cells *in vitro* (figure 17B).

One cannot extrapolate the teaching of the specification to the scope of the claims because it is unpredictable that administration of a plasminogen activator alone or in combination with captopril would be useful for treating any angiogenic disease, i.e. a disease caused by generation of new blood vessels into a tissue or organ, e.g. ocular neovascularization, arthritis, and diabetes (WO 97/41824, page 1, last paragraph).

It is noted that as disclosed in the specification, angiostatin is affinity purified from the plasma of patients, and then is used for treating growth of endothelial cells *in vitro*. It is well known in the art that affinity purification would significantly concentrate a purified protein, and thus the concentration used for reducing growth of endothelial cells *in vitro* would not reflect the concentration of angiostatin at the site of angiogenic diseases *in vivo*. Moreover, the *in vitro* condition is different and is not as complex as *in vivo* condition, wherein in *in vitro* conditions, the cells are constantly exposed to angiostatin. Further, the tested endothelial cells are not cells having angiogenesis activity. On the contrary, Berman et al, 1982, Invest Opthalmol Vis sci, 22: 191-199, clearly teach that administration of a plasminogen activator, urokinase, actually promotes vascularization of the cornea *in vivo*. Thus it is unpredictable that administration of a plasminogen activator alone would be useful for treating any angiogenic disease.

Further, although captopril inhibits angiogenesis and has been used for treating various angiogenic diseases (Volpert et al, 1996, IDS #DA, of paper No:8 on 11/21/01), the effect on angiogenesis activity by a combination of a plasminogen activator and captopril is unpredictable, because a plasminogen activator such as urokinase and captopril have opposite effects on angiogenesis activity.

Thus although an example is usually not required for 112, first paragraph rejection, but in view of the complex nature of the claimed invention, and the above unpredictability, it would have been a burden for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Meehan et al, 1995, Blood Coagulation and Fibrinolysis, 6: 105-112, or Calvo F A et al, 1992, Cancer, 70 (11): 2624-2630, as evidenced by US PN=4, 968494.

Claim 19 is drawn to a method for treating an angiogenic disease comprising administering an amount of plasminogen activator effective to convert plasminogen to plasmin, and optionally an amount of sulfhydryl donor effective to cause the conversion of plasmin to angiostatin.

Due to the language optionally, claim 19 encompasses a method for treating an angiogenic disease comprising administering an amount of a plasminogen activator alone effective to convert plasminogen to plasmin, without the administration of a sulfydryl donor.

Meehan et al teach urokinase therapy in small cell carcinoma of the lung.

Calvo et al teach urokinase combination chemotherapy.

PN=4,968494 teaches that plasminogen, an inactive precursor of plasmin, is activated by a plasminogen activator, such as urokinase, or tissue plasminogen activator, to form plasmin (column 1, lines 20-25).

Thus, although Meehan et al and Calvo et al do not teach a plasminogen activator, urokinase is inherently a type of plasminogen activator, as evidenced by PN=4,968494. In addition, although Meehan et al and Calvo et al do not teach conversion of a plasminogen to plasmin by a plasminogen activator, however, the claimed administered plasminogen appears to be the same as the prior art plasminogen. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Moreover, because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 20, 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meehan et al, *supra*, or Calvo et al, *supra*, in view of Volpert et al, *supra*, or Reddy et al, 1995, Proc Soc Exp Biol Med 210(3): 221-6 and US PN=4,968494.

Claims 19, 20, 23-24 are drawn to a method for treating an angiogenic disease comprising administering a plasminogen activator effective to convert plasminogen to plasmin, and optionally a sulfhydryl donor effective to convert plasmin to angiostatin, wherein the plasminogen activator is tissue plasminogen activator, and wherein the sulfhydryl donor is captopril. Said method further comprises administration of plasminogen.

The teaching of Meehan et al has been set forth above. Meehan et al teach urokinase therapy in small cell carcinoma of the lung, wherein the tumor is decreased in size by about 75% (p.110).

Meehan et al do not teach a method for treating an angiogenic disease comprising administering a plasminogen activator effective to convert plasminogen to plasmin, and optionally a sulfhydryl donor effective to convert plasmin to angiostatin, wherein the plasminogen activator is tissue plasminogen activator, and wherein the sulfhydryl donor is captopril. Meehan et al do not teach a method for treating an angiogenic disease comprising administering a plasminogen activator, and optionally a sulfhydryl donor, wherein plasminogen is also administered.

Calvo et al teach urokinase combination chemotherapy.

Volpert et al teach that captopril inhibits angiogenesis, and could be used for treating arthritis, diabetic retinopathy, atherosclerosis, and cancer, all of which are angiogenesis dependent (p.671, second column). In other words, cancer is an angiogenic disease.

Reddy et al teach that captopril has antimitotic activity and down regulates growth-related gene expression in pancreatic cancer cells independently of angiogenesis activity, and that the growth inhibition by captopril may occur by downregulating growth related gene expression.

PN=4,968494 teaches that plasminogen, an inactive precursor of plasmin, is activated by a plasminogen activator, such as urokinase, or tissue plasminogen activator, to form plasmin (column 1, lines 20-25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat an angiogenic disease such as cancer comprising administering a plasminogen activator, with or without administering captopril, because of the following reasons: 1) a plasminogen activator could be used to treat lung cancer, as taught by Meehan et al, and Calvo et al, 2) captopril could be used for treating a variety of angiogenic diseases, including cancer, as taught by Volpert et al, and Reddy et al, and 3) a plasminogen activor and a sulfhydryl donor such as captopril could kill tumor cells by different mechanisms, one through acting on plasminogen, and the other through downregulating growth related gene expression, and thus are complementary to each other, and in addition, a combination therapy using different drugs is common in

the art for enhancing their therapeutic effects. It would have been obvious to replace one plasminogen activator with another plasminogen activator, because they have the same property, i.e. activator of plasminogen. It would have been obvious to administer plasminogen with a plasminogen activator and a sulhydryl donor, because plasminogen is a substrate of a plasminogen activator.

In addition, although the prior art does not teach conversion of plasminogen to plasmin by a plasminogen activator, and conversion of plasmin to angiostatin by a sulfhydryl donor, however, the claimed administered plasminogen activator, and sulfhydryl donor appear to be the same as the prior art plasminogen activator and sulfhydryl donor, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

One of ordinary skill in the art would have been motivated to treat an angiogenic disease, such as cancer, comprising administering a plasminogen activator, a sulhydryl donor, and plasminogen with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

January 25, 2002

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